IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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THERAPEUTIC PROCESS FOR

INHIBITING NF-kB

BACKGROUND OF THE INVENTION

CITATION OF ART

Lee et al VIROLOGY 234 277 (1997) (Ref. AR) is a publication by Howard L. Elford, applicant in the matter of the above-entitled application and those research scientists at McGill who carried out the biological testing delineated therein. It should be noted that this publication has a received date of 5/27/97. Note also on page 280 the chemical structures of various compounds tested for their ability to inhibit the activation of NF-kB. Among these compounds are known iron chelators, antioxidants, and Applicant's ribonucleotide reductase inhibitors (hereinafter RNIs). The 3 iron chelators were inactive. Trimidox, one of Applican's compounds whose use is claimed herein, was 50 times more active than an antioxidant, N-acetylcysteine, in inhibiting NF-kB activity and HIV LTR expression.

Baeuerle and Henkel ANN. REV. IMMUN. 12 141 (1994) (Ref. BH) is an excellent review of the entire biological background of the role NF-kB plays in the immune system. As the authors state, "interference with the activation or activity of NF-kB may be beneficial in suppressing septic shock, graft-vs-host reactions, acute inflammatory reactions, acute phase response and radiation damage". The authors believe that antioxidants and specific protease inhibitors might be of use in interfering with the above acute processes, specifically that "The inhibition of NF-kB activation by antioxidants and specific protease

inhibitors may provide a pharmacological basis for interfering with these acute processes".

Schreck et al EMBO 10 2247 (1991) (Ref. AS) demonstrate that hydrogen peroxide in micromolar concentrations can induce the expression and replication HIV-1 in a human T cell line.The effect is mediated by the NF-$_k$B transcription factor. N-acetylcyteine, an antioxidant, prevented this activation. The authors suggest that diverse agents thought to activate NF-$_k$B by distinct intracellular pathways might all act by a common mechanism involving the synthesis of reactive oxygen intermediates (ROI)

Sun et al MOL. & CELL. BIOL. 16 1058 (1996) (Ref. AT) describe a group of NF-$_k$B inhibitors which lack an N-terminal sequence in I$_k$B$_a$.

Staal et al METHODS IN ENZYMOLOGY 252 168 (1995) (Ref. AU) discuss the redox regulation of NF-$_k$B transcription factor complex and the effect of N-acetylcysteine on this complex.

Ref. AF is a news report from Science Nov. 1996, which describes a series of papers and summarizes the results described therein. Reference BA gives the full text of three of these papers from the same isue of Science. The information is chiefly background information relating to the role of NF-$_k$B in preventing TNF (tumor necrosis factor) alpha induced cell death. Roederer et al Proc. Nat. Acad. Sci. USA 87 4884 (1991) (Ref. AX) discusses the inhibition of cytokine-induced hman HIV replication by N-acetylcysteine (NAC). Viral replication was stimulated by TNF + phorbol 12-myristate 13-acetate. The authors suggest that NAC be used in the treatment of AIDS.

Ref. AY, appearing in the New England Journal of Medicine 336 1066 (19970 states that NF-$_k$B is a pivotal transcription factor in chronic inflammatory disease. Specific inhibitors of NF-$_k$B

mentioned include gliotoxin and interleukin-10.

Staal et al AIDS Res. 9 299 (1993) (Ref. AV) demonstrates that antioxidants regulate NF-$_k$B activation and signal transduction pathways leading to HIV expression. N-acetylcysteine is the antioxidant used. The authors also give a number of other antioxidants that might accomplish the same end, including BHA NDGA, vit. E succinate, and reduced vit. C.

Baruchel and Wainberg J. Leuko. Biol. 52 111 (1992) (Ref.BB) discuss the activation of the AIDS virus by oxidants such as the superoxide radical, hydrogen peroxide, hydroxyl radicals and lipid peroxides . The role of antioxidants in therapeutic strategies is also discussed. These antioxidants include glutathione and its ester, NAC, pentoxyphylline, desferrioxamine, vit. C, and 2-l-oxothiazolidone.

Hauser et al CAN. RES. 50 3503 (1990) (Ref. BC) describes research dealing with the role of oxygen free-radicals on the effect of TNF in mice. The mice bore methylcholanthrene-induced sarcomas and treatment with CuZn superoxide dismutase (SOD), either bovine or recombinant human, afforded significant protection from a later challenge with TNF. Pretreatment with the dismutase increased survival time in TNF treated, but non-tumor bearing, mice. Protection from TNF tocicity with the dimutase did not affect the efficacy of TNF vs the sarcoma. The authors conclude that TNF toxicity is mediated by the release of oxygen free-radicals. The authors characterize superoxide dismutase (SOD) as a free-radical scavenger. SOD scavenges only one free radical, superoxide. Applicant's compounds scavenge many oxygen free-radicals including OH! and are thus free-radical scavengers (plural) rather than a free-radical scavenger (singular) such as SOD.

Green, in Science 278 1246 (1997) (Ref. BE) (dated 11/14/97) discusses the mechanism of apoptosis and how cell-death is suppressed.

Kumar et al ibid page 1630, (Ref. BF) discuss their finding that reintroduction of signal transducers and transcription activators ($STAT1_\alpha$) restored TNF-alpha-induced apoptosis. The authors conclude that these cells contain low levels of caspases.

Ref. BG is a Science news letter dated 4/3/98 which discusses recent research on the role of caspases in apoptosis, and in general is an excellent updating of research relating to apoptosis.

Applicant discerns nothing in the cited prior art which would either anticipate or render obvious the claims of the above-entitled application.

Respectfully submitted,

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